

University of Groningen

Motor function, paratonia and glycation cross-linked in older people

Drenth, Hans

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Drenth, H. (2018). *Motor function, paratonia and glycation cross-linked in older people: Motor function decline and paratonia and their relation with Advanced Glycation End-products*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

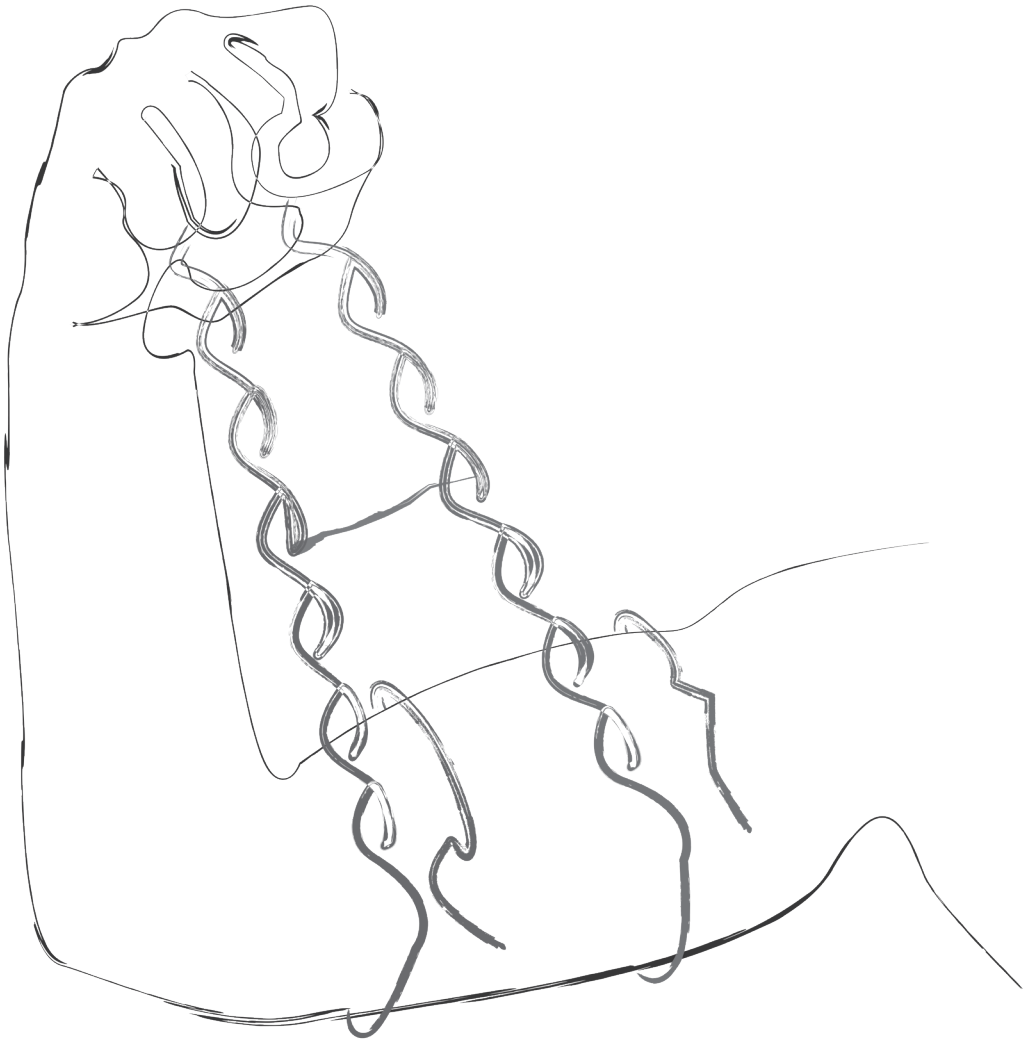
Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Chapter 7

Summary and General Discussion



Decline in motor function is a common problem in the aging population and is associated with a wide range of adverse health consequences. Different mechanisms contribute to the age-related decline in motor function. One of these that may possibly be a factor in this decline are advanced glycation end-products (AGEs). Since the early 1980s, it has been proposed that the cross-linking of long-lived proteins mediated by AGEs contributes to the age-related decline of the functioning of cells and tissues in normal aging. In addition, the decline in motor function is a consequence of age related diseases such as dementia. Focussing on dementia, motor problems are well described and are considered as an integral element of the diagnosis, however, they are less studied than the cognitive aspects. This is especially the case with paratonia, a specific form of progressive hypertonia and movement stiffness that is experienced by those individuals with dementia. Paratonia was already being described beginning 1828, however, it was not until 2006 that a consensus definition of it was established ¹. Despite this, paratonia is still fairly unknown. Although patients, clinicians, and caregivers are being confronted daily with the deterioration in motor function due to paratonia, only minimal attention is still being paid to it in current scientific literature.

The focus of this thesis was to gain insight into paratonia and general motor dysfunction by studying the potential role of AGEs, which have been described as causing mechanical stiffness and loss of elasticity in muscle tissue through collagen cross-linking and/or inflammatory processes. The results of this thesis give rise for further research into motor function decline in the aging population and paratonia in particular.

The main aims of this thesis were to study the contribution of AGEs to the decline in motor function in the aging population (**Chapters 2 and 3**) and to study the contribution of AGEs to the pathogenesis of paratonia (**Chapter 4**) and functional performance in people with dementia (**Chapter 5**). In addition, this thesis answers the question of whether the MyotonPRO is a valid and reproducible tool that can be used to objectively quantify paratonia severity in people with dementia (**Chapter 6**).

SUMMARY OF MAIN FINDINGS

Chapter 2 describes the results from the systematic review that was conducted in order to gain insight in the relationship between AGEs and motor function decline. Several studies on the relationship between AGEs and motor function have been published, however, the majority of these studies most often showed an indirect relationship. The review identified eight studies of moderate-to-good quality with a direct relationship between AGEs and motor function. The results indicated that higher levels of AGEs are independently related

to decreased walking abilities, inferior activities of daily living (ADL), diminished muscle properties, and increased physical frailty in a predominantly older population.

Chapter 3 describes the results of a cross-sectional study in 5,624 participants aged 65 years and older from the LifeLines cohort database into the direct relationship between AGE levels and motor dysfunction. In this study, we found evidence that AGEs can be an independent additional explaining factor of decreased physical activity and physical functioning.

Chapters 4 and 5 describe the results of the PARAGE (Paratonia and AGE) study. The PARAGE study was a one-year follow-up study with three measurements (baseline, after six months, and after 12 months) in 144 community dwelling individuals with early stage Alzheimer's disease (AD) or mixed dementia.

Chapter 4 describes the contribution of AGEs to paratonia. The results show that high levels of AGEs are associated with paratonia and suggest that elevated AGE levels are a contributing factor to both its presence and severity. These findings provide a new perspective on paratonia. In early stage dementia, the AGE induced biomechanical muscle tissue stiffness and elasticity loss might be the resistance that is perceived during passive movement examination (e.g., with the paratonia assessment instrument). This could mean that, besides a central cerebral factor, because of the dementia pathology, a biomechanical peripheral factor is involved in the development of paratonia.

Chapter 5 describes the contribution of AGEs to functional mobility decline and impaired activities of daily living (ADL). The study reveals a significant association between high AGE levels and a decline in functional mobility. This finding is consistent with studies describing the effect of AGEs on the decline of walking abilities and contributes to the increasing evidence that decline in functional mobility can be attributed to the effects of AGEs on muscle tissue. Although impaired muscle function - through AGEs-induced muscle damage – can probably contribute to impaired ADL, the results from the PARAGE study did not confirm this in people with early stage dementia. This could be because the sample size of 144 participants was possibly too small and a study duration of one year too brief to detect a decline in ADL, and/or the participants were less ADL independent at baseline.

Chapter 6 describes the study into the MyotonPRO, a noninvasive portable device, for measuring paratonia severity as an alternative to the modified Ashworth scale for paratonia (MAS-P). The MyotonPRO was studied regarding its validity, reproducibility and sensitivity/ responsiveness to change in dementia patients with paratonia. With the MAS-P, muscle tone is measured subjectively by the perceived resistance during passive

movement. The MyotonPRO exerts a local passive movement of the muscle and is able to objectively measure a construct of five different parameters of tone and stiffness. In this study, in dementia patients with (n=70) and without paratonia (n=82), muscle properties were assessed with the MyotonPRO by two assessors within one session and repeated by the main researcher after 30 minutes and again after six months. The results show that accurate and objective measurement of paratonia severity proves to be challenging. The MyotonPRO measurements are more precise and objective than MAS-P measurements and is potentially suitable to evaluate therapeutic interventions, cross-sectional between groups. However, because of the inherent characteristics of paratonia (e.g., variability in movement resistance) the outcomes from the MyotonPRO should be interpreted with care.

GENERAL DISCUSSION

The following section discusses the implications of the findings and the strengths and limitation of this thesis. In addition, clinical implications and future considerations are being discussed. The section will be completed with a number of final remarks.

Contribution of AGEs to Motor Function Decline

The results from this thesis contribute to the increasing evidence that AGE induced impaired skeletal muscle function, through collagen cross-linking and intramuscular inflammation, contributes to motor function decline in the aging population. AGE formation and accumulation contributes to motor function decline and to a consequential decline in physical activity. In addition, decline in physical activity is suggested to increase AGE formation and accumulation. High AGE levels can be considered as a catalyst for the deterioration of motor function and, in this way, a vicious circle is created (see Figure 5). Therefore, high AGE levels can be regarded as a biomarker and risk factor for a decline in motor function that has a subsequent negative influence on age-related diseases.

Given the mutual inter-relationship between the different structures involved in generating movement, the AGE induced damage can relate to these structures individually or even simultaneously. Therefore, besides the peripheral effect on musculoskeletal structures, AGE induced damage on peripheral neural structures could also contribute to impaired motor function by hampering neuro-muscular and/or sensory signalling processes. It also has to be considered that AGE accumulation in the central nervous system (CNS) may affect motor function. AGE accumulation in specific relevant motor-related brain regions might have an effect on the complex inter-relationship between the motor networks within the CNS for generating movement. It is even conceivable that the effect of AGEs on both central and

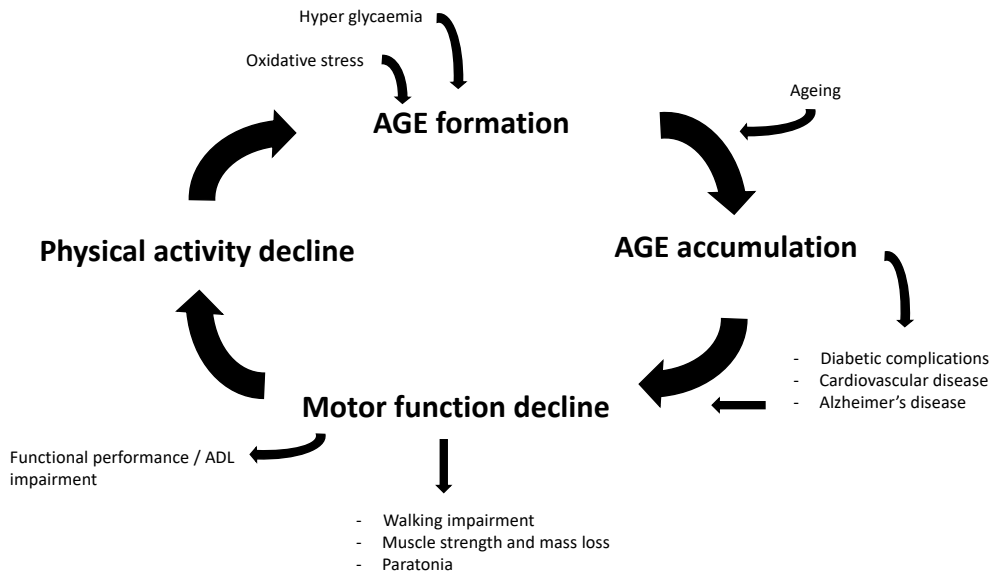


Figure 5. Vicious circle of the relationship between AGEs and motor function decline

peripheral tissue levels might even augment the decline in motor function. Future research is necessary to study this in depth.

Contribution of AGEs to Paratonia

With the novel finding that AGEs are associated with the development of paratonia, a new piece is added to the complex puzzle and contributes to the unravelling of this specific motor problem in those individuals with dementia. The most innovative finding in this thesis is that paratonia appears to be developing on a peripheral, skeletal-muscular level next to the proposed central, cerebral level. Considering the evidence, the findings confirm the hypothesis that, in early stage dementia, the slight to more marked resistance perceived during passive movement is caused by biomechanical changes because of AGE accumulation. It could be hypothesised that, in these early stages, AGE accumulation is a greater factor initiating movement stiffness and that the central cerebral factor builds up or even accelerates paratonia. Here also arises the above-described vicious circle (Figure 5) in which as a result of the progressive dementia process, motor function becomes impaired and, as a consequence, physical activity decreases, which in turn contributes to the accumulation of AGEs. This AGE accumulation again results in the progression of paratonia, and so on. Although the central factor, the cerebral damage caused by the dementia

process, seems to be the most obvious cause of paratonia in the late stages of dementia, we still have little insight into these central mechanisms on paratonia. Severe paratonia, as evidenced by high resistance during movement or active opposition, is especially seen in the later stages of dementia. In these severe stages of dementia, paratonia has been associated with the return of primitive neonatal reflexes ^{2,3}. Also, clinicians and caregivers who deal in daily practice with patients suffering from paratonia have observed that movement stiffness and active opposition (described as gegenhalten ⁴) during ADL can vary and may occur at random moments. Factors such as aggression, agitation, anxiety, pain, and confusion, but also sudden external stimuli (e.g., light, sound) are noticed as influencing paratonia. AGEs may possibly be involved in the central factor causing paratonia because interaction between AGEs, Amyloid-beta, and tau-protein have been described to affect neuronal function ⁵. When these neuronal functions are affected in motor function related areas, they may possibly contribute to the pathogenesis of paratonia.

The findings in this thesis suggests that both peripheral and central, AGE induced, damage contribute to the pathogenesis of paratonia. Therefore, targeting AGE accumulation is imperative.

Clinical Implications for the General Aging Population

To prevent AGE induced tissue damage, the inhibition of the formation and accumulation of AGEs might be a factor to reduce or postpone motor function decline in the aging population. Approaches to prevent AGE formation or AGE accumulation can be divided into: pharmacologic, dietary, and exercise strategies. Pharmacologic strategies on AGE formation inhibition and cross-link breaking are being studied, however, results show conflicting evidence, therefore, none of the results can currently be used clinically ⁶. A restricted intake of AGEs is a possible factor to reduce the AGE burden in the human body. AGEs are present in foods that have undergone the chemical Maillard-reaction that occurs in frying, grilling, broiling, and roasting. A diet low on AGEs is shown to decrease the levels of circulating AGEs and may possibly prevent inflammation and age related diseases, however, evidence of the harmful effects of long-term exposure to dietary AGEs is still inconclusive ⁷.

The glycation process is accelerated by the excessive elevation of glucose concentration and oxidative stress. Removing these accelerators through intensive glycaemic control and reducing oxidative stress may be the key-method for decreasing AGEs formation. Glucose intake can be influenced by nutrition, and physical activity and exercise has demonstrated that it reduces glycation and oxidative stress and thereby consequently reducing AGE formation ^{8,9}.

The negative effect of AGEs on motor function already begins during midlife and, as AGE levels increase with aging, therefore, an elevated AGEs level as a biomarker could predict a decline in motor function later in life. Elevated AGE-levels can be detected at an early stage fairly easily and non-invasively by using an AGE-reader. This could occur, for example, during regular check-ups at the general practitioner or possibly as a self-assessment. In this way, an increased risk of AGEs-related diseases such as cardio-vascular diseases and the risk of motor function decline can also be detected. Preventive interventions on AGE reduction, therefore, should begin as soon as possible as part of healthy aging.

Clinical Implications for Dementia Patients With and Without Paratonia

The studies in this thesis involving individuals with paratonia show that, in the early stages of dementia, the variability in movement resistance is frequently present. This is in accordance with previous paratonia studies. This variability suggests that paratonia can be influenced. It is suggested that the phenomenon of active assistance (described as *mitgehen*³) or the inability to relax could be seen as a precursor of active resistance or severe paratonia³. It could be hypothesized that, when this active assistance is observed together with an increased AGE level, the risk of developing paratonia increases. Targeting AGE accumulation early on, preventing peripheral musculoskeletal tissue damage, and even influencing damage in the CNS might be a method to combat paratonia.

As mentioned earlier, the effects of paratonia hamper motor function already in the early stages but, in the late stages of dementia, the effects of paratonia are devastating. Daily, clinicians and caregivers of people with dementia who experience paratonia must deal with the consequences of paratonia. In the Netherlands, practice-based interventions such as stabilizing cushions, special bed mattresses, and the concept of Passivity in Daily Life (PDL) are used, however, scientific evidence of any effects is lacking. Several years ago, passive movement therapy was the primary physiotherapeutic intervention but proved to be ineffective and even harmful for patients with paratonia in the severe stages of dementia¹⁰. These findings resulted in physiotherapists being no longer, or much less, involved with motor problems in individuals with dementia in health care institutions (nursing homes and small-scale living accommodations).

In the Netherlands, the elderly population in these health care institutions are structurally physically inactive¹¹. Given the fact that still no effective interventions are available to prevent or postpone paratonia, the lack of physical activity and reduced involvement of the physiotherapists in these health care institutions is an undesirable development. Because of the positive effects of exercise on the formation of AGEs, next to the effect on physical

functioning and performance, the physiotherapist should be involved in this frail group of elderly people with dementia. In this way, tailor-made exercise programs can be made and motor function decline (e.g., paratonia) could be prevented or postponed.

Future Considerations

The results of the studies presented in this thesis gives rise to several in depth future considerations.

Motor function decline in pre-clinical dementia

The most common cause of dementia is Alzheimer's disease (AD) which is usually associated with a progressive decline in cognitive function, especially memory loss. AD is characterized by amyloid plaques and neurofibrillary tangles that are present in high numbers in the grey matter of the affected brain. AGEs have been shown to be associated with lower grey matter volume and to be accumulating in brain tissue and are suggested to explain many biochemical and neuropathological changes in AD ^{5,12,13}. In addition to cognitive decline, accompanying decline in motor function is frequently reported and is one element of the dementia diagnosis. It has been ascertained that, several years prior to the dementia diagnosis, motor function decline is already observed in pre-clinical people with dementia compared to the control group ¹⁴. Several authors suggest that a decline in motor function and/or a lower level of physical activity are risk factors for future AD ^{15–19}. However, examining the literature of the potential role of AGEs in AD combined with the findings on the role of AGEs on motor function raises an interesting question: Is motor function decline a first sign of dementia or is it a risk factor for getting dementia? Either way, as already mentioned, motor function decline resulting in decline in physical activity increases AGE accumulation that subsequently has a negative effect on motor function. Because this motor function decline can precede cognitive impairment by several years, it is important to detect these high AGE levels as early as possible in order to prevent further decline in motor function. It could even be hypothesized that lowering AGE levels may possibly contribute to postponing or slowing down the dementia process. Therefore, future research is necessary to study the long-term effect of AGEs on the different types of dementia.

The early motor function decline in mild cognitive impairment and early dementia presents itself, among other things, with slow, unsteady, and stiff movements that could be the result of biomechanical changes caused by AGEs. In this context, it would be interesting to study if this movement stiffness is already present in the general older population without dementia or is this movement stiffness specific for people with dementia where AGEs accumulation is accelerated, and this movement stiffness is (an early form of) paratonia. This could also

contribute to unravelling the peripheral and/or central component of paratonia. Hence, it would be important to study the presence of movement stiffness and the relationship with high AGE levels in older people without dementia.

Re-evaluating paratonia

The results from this thesis gives rise to re-evaluate the current state regarding paratonia. For example, differentiation between the broad spectrum of severe hypertonia to active opposition during passive movement and movement stiffness due to biomechanical muscular changes may possibly be necessary. This is especially important for future studies into effective interventions. Severe hypertonia and active opposition may require other interventions than peripheral biomechanical changes.

For diagnosing paratonia, the paratonia assessment instrument (PAI) is the only valid measurement available where the severity of the perceived resistance during the PAI is scored with the modified Ashworth scale for paratonia (MAS-P). Still, diagnosing paratonia proves to be challenging and experience is necessary, especially for detecting slight movement resistance during assessment with the PAI. Therefore, future research should also study and develop instruments that are more objective to diagnose paratonia.

The results of the MyotonPRO study may provide an impetus to study whether the MyotonPRO is suitable for the diagnosis of paratonia. In the study with the MyotonPRO, it was established that it was able to discriminate participants with and without paratonia. Because of the sensitivity and specificity values that were found, the MyotonPRO cannot yet be recommended for diagnosing paratonia. Using medical imaging technology such as functional magnetic resonance imaging (fMRI) in future studies in people with dementia could provide more clarity on which brain regions are involved in paratonia. Further studies with the MyotonPRO, possible in combination with fMRI technology, could lead to an objective instrument to diagnose paratonia. Using the MyotonPRO as an alternative for the subjective MAS-P has potential; however, future studies should focus on additional guidelines for MyotonPRO measurements, for example, multiple measurements during a period of time similar to blood pressure measurement. This could possibly adjust for the diurnal variation of paratonia and increase the clinical interpretation and improve reproducibility. Until the time that objective measuring instruments are available to measure the presence and severity of paratonia, it is recommended that, for subsequent studies involving paratonia, multiple outcome measures are measured on different domains (e.g., functional, behavioural, care burden) together with the PAI.

AGE targeting

A combined approach of dietary and physical exercise possibly in combination with future drug therapy might be the most effective way of targeting AGE formation, also because the multidisciplinary approach in glycaemic control has proven to be effective in diabetes patients. Future studies on targeting AGE levels, therefore, should include these multidisciplinary interventions.

Regular physical activity is considered to be effective for maintaining health or preventing disability in general, however, the underlying physiological pathways remain unclear. The results from this thesis provide indications for AGE accumulation reduction to contribute to health maintenance. The exact way in which AGEs play a role has yet to be further investigated. For example, it remains unclear what these physical activities should entail and at what frequency and at what intensity level they should be done in order to reduce AGE accumulation. It is, therefore, important that future research examines the modalities of physical activity and exercises that significantly reduce AGE levels in the aging population in general and specifically for people with dementia. This may include low or high intensity strength and/or endurance exercises or maybe simple, everyday physical activities. This would help to provide specific, customized advice and exercises which is especially important because combating central AGE accumulation may require different exercise modalities than combating peripheral AGE accumulation. Even cross-linking AGEs may require a different approach than non-cross-linking AGE.

Strengths and Limitations

Motor function, and specifically paratonia, in people with dementia has only been minimally studied while the consequences have such a significant impact on the quality of life of the patient and the caregiver. A major strength of this thesis is that, with the PARAGE and MyotonPRO study, we had the opportunity to longitudinally study a large cohort of people with dementia in different settings throughout the Netherlands. The limitation of the majority of studies in this thesis studying the relationship between motor function and AGEs is that a causal relationship cannot be inferred. The results demonstrate that high AGE levels are associated with several motor function impairments in the aging population and with paratonia and decline in functional performance in people with dementia. Future studies should focus on investigating AGE targeted interventions on motor function, which could be considered as a proof of concept underpinning the causal relationship of AGEs and decline in motor function.

FINAL REMARKS

Glycation, the spontaneous non-enzymatic reaction of sugars with proteins and lipids that results in AGEs is a topic of increasing importance in human health. There is growing evidence that AGEs play an important role in aging and age-related diseases. This thesis shows that there are strong indications that AGE induced protein damage, collagen cross-links, and inflammatory processes leading to musculoskeletal tissue impairment as well as peripheral and central neural function loss contributes to the age-related decline in motor function.

With the indications from this thesis that AGEs are involved in the pathogenesis of paratonia, we finally have something with which to pursue further research in combating paratonia, at least in the early stages of dementia, which might possibly prevent severe paratonia. The results of this thesis are a starting point for further research into the relationship between AGEs and paratonia to keep people with dementia independent longer and improve quality of life and daily care of patients suffering from paratonia.

Finally, it is beneficial to reflect on the fact that the population of Western countries is aging. This is consequently accompanied by having a greater number of chronic diseases and places extensive burdens on health care finances ²⁰. There is growing evidence that preventive measures such as exercise and healthy diet as part of a healthy lifestyle reduce the risk on and improve the prognosis of chronic diseases. The results from this thesis contribute to this by providing evidence for the role of AGEs as a risk factor for motor function decline and, as a consequence, decline in functioning and risk on age-related diseases. Therefore, it is important that preventive measures on lowering AGEs begin as soon as possible. This also means that healthcare and health insurance companies should invest in these preventive, relatively low-cost interventions.

REFERENCES

1. Hobbelen JSM, Koopmans RTCM, Verhey FRJ, Van Peppen RPS, de Bie RA. Paratonia: a Delphi procedure for consensus definition. *J Geriatr Phys Ther.* 2006;29(2):50-56.
2. Vahia I, Cohen CI, Prehogan A, Memon Z. Prevalence and impact of paratonia in Alzheimer disease in a multiracial sample. *Am J Geriatr Psychiatry.* 2007;15(4):351-353. doi:10.1097/JGP.0b013e31802ea907.
3. Beversdorf DQ, Heilman KM. Facilitory paratonia and frontal lobe functioning. *Neurology.* 1998;51(4):968-971.
4. Kleist, K. Gegenhalten (motorischer Negativismus) Zwanga greifen und Thalamus Opticus. *Monatschr Psychiat Neurol.* 1927;65:317.
5. Rahmadi A, Steiner N, Munch G. Advanced glycation endproducts as gerontotoxins and biomarkers for carbonyl-based degenerative processes in Alzheimer's disease. *Clin Chem Lab Med.* 2011;49(3):385-391.
6. Nenna A, Spadaccio C, Lusini M, Ulianich L, Chello M, Nappi F. Basic and Clinical Research Against Advanced Glycation End Products (AGEs): New Compounds to Tackle Cardiovascular Disease and Diabetic Complications. *Recent Adv Cardiovasc drug Discov.* 2015;10(1):10-33.
7. Puyvelde K Van, Mets T, Njemini R, Beyer I, Bautmans I. Effect of advanced glycation end product intake on inflammation and aging: a systematic review. *Nutr Rev.* 2014;72(10):638-650.
8. Ahmed N, Thornalley PJ. Advanced glycation endproducts: what is their relevance to diabetic complications? *Diabetes, Obes Metab.* 2007;9(3):233-245.
9. Magelhaes PM, j. Appell H, Duarte JA. Involvement of advanced glycation end products in the pathogenesis of diabetic complications: the protective role of regular physical activity. *Eur Rev Aging Phys Act.* 2008;(5):17-29.
10. Hobbelen JHSM, Tan FES, Verhey FRJ, Koopmans RTCM, de Bie RA. Passive movement therapy in severe paratonia: a multicenter randomized clinical trial. *Int psychogeriatrics.* 2012;24(5):834-844. doi:10.1017/S1041610211002468.
11. Hiemstra A. *Factsheet Belang van Bewegen Voor Ouderen.* Ede; 2016.
12. Li J, Liu D, Sun L, Lu Y, Zhang Z. Advanced glycation end products and neurodegenerative diseases: mechanisms and perspective. *J Neurol Sci.* 2012;317(1-2):1-5. doi:10.1016/j.jns.2012.02.018.
13. Spauwen PJJ, van Eupen MGA, Kohler S, et al. Associations of advanced glycation end-products with cognitive functions in individuals with and without type 2 diabetes: the maastricht study. *J Clin Endocrinol Metab.* 2015;100(3):951-960. doi:10.1210/jc.2014-2754.
14. Ramakers IHGB, Visser PJ, Aalten P, et al. Symptoms of preclinical dementia in general practice up to five years before dementia diagnosis. *Dement Geriatr Cogn Disord.* 2007;24(4):300-306. doi:10.1159/000107594.
15. Camicioli R, Howieson D, Oken B, Sexton G, Kaye J. Motor slowing precedes cognitive impairment in the oldest old. *Neurology.* 1998;50(5):1496-1498.
16. Buchman AS, Bennett DA. Loss of motor function in preclinical Alzheimer's disease. *Expert Rev Neurother.* 2011;11(5):665-676.
17. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The trajectory of gait speed preceding mild cognitive impairment. *Arch Neurol.* 2010;67(8):980-986. doi:10.1001/archneurol.2010.159.
18. Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. *Arch Intern Med.* 2006;166(10):1115-1120. doi:10.1001/archinte.166.10.1115.

19. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Arch Neurol*. 2006;63(12):1763-1769. doi:10.1001/archneur.63.12.1763.
20. W.H.O. *World Report on Ageing and Health 2015*. Geneva; 2015.

